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Comparison of intranasal administration of diazepam, midazolam and xylazine in Pigeons: Clinical evaluation

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Abstract

Safe and effective sedation methods are as much important for small pet birds as for the other animals not only for surgical procedures but also for safe handling and diagnostic and clinical procedures such as radiography, wound dressing, blood collection, endoscopy and fracture repair procedures. The aim of this study is comparison of sedation efficacy in intranasal administration of xylazine, diazepam and midazolam in Pigeons. Fifteen healthy adult domesticated Pigeons of both sexes, weighing 289±61.8 gram were used in this study.

Xylazine (29.4±1.9 mg/kg), diazepam (6.4±0.9 mg/kg) and midazolam (6.5±1.0 mg/kg) was administered intranasaly using a micropipette. The onset time, dorsal recumbency duration time and duration of sedation time were measured and recorded.

This study showed that intranasal (IN) drug administration could provide fast and reliable sedation in Pigeons and IN midazolam or diazepam can provide adequate sedation for diagnostic and minor therapeutic procedures.

Key words: intranasal, Diazepam, Midazolam, Xylazine, pigeon

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Introduction

Avian anaesthetic and surgical techniques have progressed greatly in the last decade. Anaesthesia procedures for avian species are different from those in domestic mammalian species. Some physiological differences among avian species should be also taken into consideration when choosing an anaesthetic drug. The anatomical localization of the trachea, alterations in gas exchange and ventilation of the avian pulmonary system have been considered as disadvantages (Uzun et al., 2003). Many avian practitioners routinely perform a variety of surgical procedures, including exploratory surgery, fracture repair and surgical sexing (Bennett and Kuzma, 1992, Redig and Roush, 1987). The choice of anaesthesia and administration is often as important for success as the surgical procedure itself (Forbes, 1998). Anaesthetics are administered either as gas or injectable. Injectable anaesthetics and sedatives can be placed in vein, muscle or intraosseous (Altman, 1980, Harrison, 1986). Inhalation anaesthesia is preferred for birds but requires expensive equipment. The use of an injectable in comparison with an inhalant anaesthetic agent may have the advantage of increased speed of induction of anaesthesia, the need for minimal equipment and low cost (Forbes, 1998). However, intravenous injection is difficult and so the intramuscular (IM) or subcutaneous routes are preferred. Pectoral muscle injection was used routinely, however attempted pectoral muscle injection causes the risk of accidental intravascular or intracoelomic drug administration (Harrison, 1986, Kamiloglu et al., 2007). Injections into the thigh muscles of small birds are not recommended because of the potential for nerve damage. Pain associated with IM injection may be considerable, particularly with irritant agents. The intranasal (IN) administration of anaesthetics, alone or in combination, has been reported in adult rabbits (Robertson and Eberhart, 1994). Recently, intranasal administration of xylazine, midazolam and diazepam for sedation in canaries has been reported by Vesal et al (2006) without any complications (Vesal and Zare, 2006a, Vesal and Zare, 2006b). The aim of this study was to determine whether IN benzodiazepines (midazolam and diazepam), α2-agonists (xylazine) were effective in pigeon.

Materials and methods

Animals

Fifteen healthy adult domesticated Pigeons of both sexes, weighing 289±61.8 gram were used in this study. All birds were kept in a temperature-controlled environment (18–20 ºC) with groups of five birds per cage. The birds were clinically healthy with a normal cloacal temperature, apparently active in motion and have no sign of any gastrointestinal disorders. They were adapting for at least 3 weeks before the study began. The research protocol for this experiment was approved by the Shahrekord University research committee.

Anaesthetic protocols

Xylazine (29.4±1.9 mg/kg, Darou pakhsh, Iran), diazepam (6.4±0.9 mg/kg, Darou pakhsh, Iran) and midazolam (6.5±1.0 mg/kg, Darou pakhsh, Iran) was administered intranasaly using a micropipette (Varipet 4810; Eppendorf, Hamburg, Germany). Xylazine was administered at doses that have been studied in canaries by Vesal et al (2006) and an attempt was made to determine the dose of diazepam and midazolam that allowed sedation in pigeons. The determined dosage for diazepam and midazolam were as well as half determined dose of these drugs in canaries (Vesal and Zare, 2006a, Vesal and Zare, 2006b) . Each bird received each of three treatments at three weeks intervals randomly. All drugs were administered over approximately 30 seconds intranasaly. Immediately, after drug administration, each bird was placed in dorsal recumbency in

separate cages for observation. Noise, movement and other stimuli were minimized after drug administration. The onset time, the duration of dorsal recumbency time and duration of sedation were measured and recorded. Time from the intranasal administration of drug to loss of the consciousness was considered as time of the onset of the sedation. Time from the laying in dorsal recumbency to returning to sternal recumbency was considered duration of dorsal recumbency (The birds did not move when placed in dorsal recumbency). Time between loss and reappearance of consciousness was considered as duration time of sedation. The observer blinded to the treatment individually evaluated the sedation.

Statistic analysis

ANOVA test was used for comparison of paired data (onset and duration of sedation and duration of dorsal recumbency) followed by Duncan's test where appropriate. Statistical significance was set at $p<0.05$ and data were expressed as the mean and standard deviation (±SD) (computer program Spss, Analytical soft ware, version 15.00).

Table 1. Time to onset and duration of sedation and dorsal recumbency (mean ± SD) with each drug treatment

	Xylazine	Diazepam	Midazolam
Onset time	6.4±2.1	5.4±1.1	3.2±1.3 *
Duration of dorsal recumbency		46.8±6.3	23.4±3.7†
Duration of sedation	254.8±26.1	133±13.5‡	82.0±6.2§

*means statistical differences between onset time of midazolam with diazepam and xylazine
†means statistical differences between dorsal recumbency time of midazolam with diazepam
‡means statistical differences between duration sedation of diazepam with xylazine and midazolam
§ means statistical differences between duration sedation of midazolam with diazepam and xylazine

Results

Following intranasal administration of xylazine, diazepam and midazolam, sedation was produced in all birds. Time to onset of sedation was significantly ($p<0.05$) faster following midazolam (3.2±1.3 min) in comparison to xylazine (6.4±2.1 min), but there is not any significant differences ($p>0.05$) between midazolam versus diazepam (5.4±1.1 min) and xylazine versus diazepam. Dorsal recumbent was not observed after intranasal administration of xylazine. Significantly ($p<0.05$) shorter duration of dorsal recumbency was observed following midazolam administration (23.4±3.7min) in comparison of diazepam administration (46.8±6.3). Xylazine produced significantly ($p<0.05$) longer duration of analgesia (254.8±26.1 min) than that produced by diazepam (133.0±13.5) and midazolam (82.0±6.2). In addition, diazepam produced significantly ($p<0.05$) longer duration of sedation than that produced by midazolam (Table1).

Intranasal administration of drugs in pigeons was accepted method without any resistance. The birds that received the diazepam or midazolam had appetite increasing after sedation had disappeared. No adverse reactions or complications were encountered after IN drug administration in this study.

Discussion

The dose of xylazine was chosen according to previous study on Canaries and an attempt was made to determine the dose of diazepam

and midazolam that allowed sedation in pigeons, were half dose using of these drugs in canaries (Vesal and Zare, 2006a, Vesal and Zare, 2006b) . Our study is a first study on intranasal administration of xylazine, diazepam and midazolam for pigeons' sedation.

Xylazin is a non-narcotic, sedative, muscle relaxant and analgesic alpha-2-

adrenergic agonist that has been used in wide range of wild and domestic animals

and birds (Ali et al., 1987, Allen and Oosterhuis, 1986, Valverde et al., 1990, Varner et al., 2004, Vesal and Eskandari, 2006a, b).

Like other benzodiazepines, midazolam acts on the benzodiazepine binding site of GABAA receptors. When bound it enhances the binding of GABA to the GABAA receptor which results in inhibitory effects on the central nervous system(Skerritt and Johnston, 1983). Midazolam has the advantage of water solubility and a shorter duration of action and is slightly more potent than diazepam and has minimal cardiopulmonary effects(Ludders and Matthews, 1996). Midazolam given intranasaly is as safe and effective as diazepam given intravenously in

management of febrile seizures in children. Intramuscular injection caused no significant changes in cardiopulmonary function in Canada geese, pigeons and quail (Day and Roge, 1996, Smith and Muir, 1992, Valverde et al., 1990). Intranasal midazolam has been successfully used for pre-anaesthetic sedation in children, as it avoids the discomfort associated with IV or IM injection. Mild side effects such as transient burning sensation and lacrimation have been reported, which

may result from its low pH (approximately 3.0–3.5). Olfactory activity was not affected in children(Bell, 1990, Ng and Shah, 2006). Midazolam given intravenously or intramuscularly is not associated with respiratory changes, although there are reported associations with hypertension, bradycardia, and hypoxia in adults and children. These changes were, however, mild and transient. No patient had to be intubated or mechanically ventilated (Koul et al., 1997, Lahat et al., 1992). Intranasal midazolam decreased the respiratory rate in rabbits but had no effect on haemoglobin saturation or on the values of venous blood gas variables. Changes in arterial oxygen saturation have not been observed following IN midazolam administered in children (Karl et al., 1992a, Karl et al., 1992b, Wilton et al., 1988). The mean onset and duration of sedation following IN midazolam in pigeons in our study were significantly shorter than two other groups. It has been proved that midazolam is extremely short act agent in comparison with diazepam (Mendelson, 1992). In addition in a recent study by Vesal et al, proved that onset of sedation following intranasal administration of midazolam was shorter than diazepam and xylazine (Vesal and Zare, 2006a, Vesal and Zare, 2006b), these finding confirmed the results of our study. Diazepam had long duration of sedation in comparison with midazolam in IN administration. Vesal et al also showed that duration of anaesthesia with diazepam was longer than midazolam in canaries. Diazepam is highly lipid-soluble, and is widely distributed throughout the body after administration and it can redistributed into muscle and adipose tissue (Bateson, 2002). We proposed that diazepam accumulate in adipose tissues and redistribute through the body therefore duration of anaesthesia was longer in diazepam administration in comparison with midazolam.

Dorsal recumbency was not observed by administration of xylazine but it observed by midazolam and diazepam administration in pigeons. This sign also was observed by Vesal et al (2006) in intranasal administration of xylazine in canaries (Vesal and Zare, 2006a,

Vesal and Zare, 2006b) . Probably midazolam and diazepam have some unknown effects on CNS that xylazine has not these mechanisms of action.

Recovery from IN xylazine took hours. Furthermore, the feathers appeared windswept in birds receiving xylazine, which remained lethargic for prolonged periods. In contrast, birds recovering from midazolam or diazepam were alert and appeared to be hungry. There were no complications associated with the prolonged recovery following xylazine administration, but these were nevertheless felt to be undesirable: by preventing eating, hypothermia and hypoglycaemia resulting from the bird's high metabolic rate is likely to be aggravated (Coles, 1997, Harrison, 1986). With α 2-agonists such as xylazine the degree of sedation may be insufficient to perform a procedure. In addition, α 2-agonists cause bradycardia and partial atrioventricular heart block, respiratory depression and muscle tremors in most species (Ludders and Matthews, 1996). However physiologic data were not recorded in our study. All pigeons had a smooth recovery and did not show signs of respiratory distress during sedation.

Conclusion

In conclusion, either midazolam or diazepam intranasal administration resulted in a satisfactory sedation in pigeons. However, midazolam intranasal administration provided a more rapid and effective sedation and might be useful for the birds requiring urgent operation.

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References

Ali, B. H., J. L. Silsby, and M. E. el Halawani. 1987. The effect of magnesium aspartate, xylazine and morphine on the immobilization-induced increase in the levels of prolactin in turkey plasma. J Vet Pharmacol Ther 10:119-126.

Allen, J. L. and J. E. Oosterhuis. 1986. Effect of tolazoline on xylazine-ketamine-induced anesthesia in turkey vultures. J Am Vet Med Assoc. 189:1011-1012.

Altman, R. B. 1980. Avian anaesthesia. Compend. Contin. Educ. Pract. Vet. 2:38-42.

Bateson, A. N. 2002. Basic pharmacologic mechanisms involved in benzodiazepine tolerance and withdrawal. Current Pharmaceutical Design. 8:5-21.

Bell, G. D. 1990. premedication and intravenous sedation for upper gastrointestinal endoscopy. Alimentary Pharmacology & Therapeutics. 4:103-122.

Bennett, R. A. and A. B. Kuzma. 1992. Fracture management in birds. J Zoo Wild Med 23:5-38.

Coles, B. H. 1997. Avian Medicine and Surgery. Blackwell Science, Oxford, UK.

Day, T. K. and C. K. Roge. 1996. Evaluation of sedation in quail induced by use of midazolam and reversed by use of flumazenil. J Am Vet Med Assoc 209:969-971.

Forbes, N. A. 1998. Avian anesthesia. Vet Q. 20:265-266.

Harrison, G. J. 1986. Anesthesiology. *in* Clinical Avian Medicine and Surgery. J. Harrison and L. R. Harrison, eds. WB Saunders, Philadelphia.

Kamiloglu, A., G. Atalan, and N. N. Kamiloglu. 2007. Comparison of intraosseous and intramuscular drug administration for induction of anaesthesia in domestic pigeons. Research in Veterinary Science. 85:171-175.

Karl, H., A. Keifer, J. L. Rosenberger, M. Larach, and J. Ruffle. 1992a. Comparison of the Safety and Efficacy of Intranasal Midazolam or Sufentanil for Preinduction of Anesthesia in Pediatric Patients. CLINICAL INVESTIGATIONS. Anesthesiology. 76(2):209-215.

Karl, H., A. Keifer, J. L. Rosenberger, M. Larach, and J. Ruffle. 1992b. Comparison of the Safety and Efficacy of Intranasal Midazolam or Sufentanil for Preinduction of Anesthesia in Pediatric Patients.CLINICAL INVESTIGATIONS. Anesthesiology. 76:209-215.

Koul, R. L., G. R. Aithala, A. Chacko, R. Joshi, and M. S. Elbualy. 1997. Continuous midazolam infusion as treatment of status epilepticus. Archives of Disease in Childhood 76:445.

Lahat, E., M. Aladjem, G. Eshel, T. Bistritzer, and Y. Katz. 1992. Midazolam in treatment of epileptic seizures. Pediatr Neurol. 8:215-216.

Ludders, J. W. and N. Matthews. 1996. Anesthesia and immobilization of specific species: Birds. Pages 645-646 *in* Veterinary anesthesia. Lumb and Jones, eds. Williams & Wilkins Verlag, Baltimore.

Mendelson, W. B. 1992. Clinical distinctions between long-acting and short-acting benzodiazepines. J Clin Psychiatry. 53:4-7.

Ng, E. and V. Shah. 2006. Benzodiazepines for Sedation in Infants and Children. Pages 170-183 *in* Sleep And Sleep Disorders: A Neuropsychopharmacological Approach. H. Lader, D. P. Cardinali, and S. R. Pandi-Perumal, eds. Springer, London.

Redig, P. T. and J. C. Roush. 1987. rthopaedic and soft tissue surgery in raptorial species. Pages 246-253 *in* Zoo and Wild Animal Medicine. M. E. Fowler, ed. WB Saunders, Philadelphia.

Reynolds, W. T. 1983. Unusual anaesthetic complication in a pelican. Veterinary Record 113:204.

Robertson, S. A. and S. Eberhart. 1994. Efficacy of the intranasal route for administration of anesthetic agents to adult rabbits. Lab Anim Sci. 44:159-165.

Samour, J. H., D. M. Jones, J. A. Knight, and J. C. Howlett. 1984. Comparative studies of the use of some injectable anaesthetic agents in birds. The Veterinary Record. 115:6-11.

Skerritt, J. H. and G. A. Johnston. 1983. Enhancement of GABA binding by benzodiazepines and related anxiolytics. Eur J Pharmacol. 89:193-198.

Smith, J. and W. W. Muir. 1992. Cardiopulmonary effects of midazolam and flumazenil in racing pigeons. Vet Surg. 21:499.

Uzun, M., S. Yildiz, G. Atalan, M. Kaya, and N. Sulu. 2003. Effects of Medetomidine-Ketamine Combination Anaesthesia on Electrocardiographic Findings, Body Temperature, and Heart and Respiratory Rates in Domestic Pigeons. . Turk J Vet Anim Sci 27:377-382.

Valverde, A., V. L. Honeyman, D. H. Dyson, and A. E. Valliant. 1990. Determination of a sedative dose and influence of midazolam on cardiopulmonary function in Canada geese. Am J Vet Res. 51:1071-1074.

Varner, J., K. R. Clifton, S. P. Bs, J. R. Broderson, and R. D. Wyatt. 2004. Lack of Efficacy of Injectable Ketamine with Xylazine or Diazepam for Anesthesia in Chickens. Lab Animal. 33:36-39.

Vesal, N. and M. H. Eskandari. 2006a. Sedative effects of midazolam and xylazine with or without ketamine and detomidine alone following intranasal administration in Ring-necked Parakeets. Journal of the American Veterinary Medical Association. 228(3):383-388.

Vesal, N. and M. H. Eskandari. 2006b. Sedative effects of midazolam and xylazine

with or without ketamine and detomidine alone following intranasal administration in Ring-necked Parakeets. Journal of the American Veterinary Medical Association. 288:383-388.

Vesal, N. and P. Zare. 2006a. Clinical evaluation of intranasal benzodiazepines, α2-agonists and their antagonists in canaries. Veterinary Anaesthesia and Analgesia. 33:143-148.

Vesal, N. and P. Zare. 2006b. Clinical evaluation of intranasal benzodiazepines, α2-agonists and their antagonists in canaries. Veterinary Anaesthesia and Analgesia. 33:143-148.

Wilton, N. C., J. F. Leigh, D. Rosen, and U. Pandit. 1988. Preanesthetic Sedation of Preschool Children Using Intranasal Midazolam.CLINICAL REPORTS. Anesthesiology 69:972-974.

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مقایسه تجویز داخل بینی دیازپام، میدازولام و گزیلازین در کبوتر: ارزیابی بالینی

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چکیده

روش‌های بیهوشی موثر و ایمن در برنده‌های کوچک خانگی مانند سایر حیوانات برای انجام معاینه، تشخیص و اعمال درمانگاهی مانند رادیوگرافی، بانسمان زخم، خونگیری، اندوسکوبی و روش‌های ترمیم شکستگی بسیار مهم هستند. هدف این مطالعه مقایسه کارایی بیهوشی حاصل از تجویز داخل بینی گزیلازین، دیازپام و میدازولام در کبوترها است. در این مطالعه ۱۵کبوتر خانگی بالغ و سالم از هـر دو جـنس بـا وزن ۶۱/۸ ± ۲۸۹ مورد استفاده قرار گرفتند. گزیلازین (۱/۹ ± ۴/ ۲۹ گـرم بـه ازای هرکیلـوگرم) ، دیازپـام (۰/۹ ± ۴/ ۶ گـرم بـه ازای هرکیلوگرم) ، میدازولام (۱ ± ۵/ ۶ گرم به ازای هرکیلوگرم) بوسیله میکروپیپت در داخل بینی تجویز شد. زمان وقوع، طول دوره خوابیدن به پشت و طول دوره بیهوشی اندازه گیری و ثبت شد. این مطالعه نشان داد که تجویز دارو در داخل بینی کبوترها مـی‌توانـد بیهوشـی سـریع و مطمئنی را ایجاد نموده و تجویز دیازپام و میدازولام می‌تواند بیهوشی مناسبی را برای اعمال تشخیصی و درمانی مختصر فراهم آورد.

واژه‌های کلیدی: داخل بینی، دیازپام ، میدازولام ، گزیلازین، کبوتر